CUSPE Cambridge University Science and Policy Exchange

CJSP Cambridge Journal of Science & Policy

The Future of Miniaturised Organs in Drug Development and Testing

COMMUNICATION | EDITORIAL | INVITED CONTRIBUTION | PERSPECTIVE | REPORT | REVIEW

Timothy S. Chisholm
Department of Chemistry
University of Cambridge

ABSTRACT

Drug development is time consuming and expensive, partly due to the difficulty of determining the safety and effectiveness of drugs in humans. To improve this process, there is a demand for models appropriate for studying the biological effects of drugs early in their development. This article considers miniaturised organ technology to evaluate the safety and efficacy of medicines and reduce our dependence on animal testing. Testing drugs on miniaturised organs could also help account for systematic biases in clinical trial populations. However, ethical concerns exist including patient consent and the anonymisation of tissue donations. This article considers these key concerns and provides policy recommendations for the ethical and responsible use of miniaturised organ technology.

SCIENCE ⇒ POLICY

Miniaturised organs grown from human tissue are showing promise as tools to test drug safety and efficacy. This technology could reduce the need for animal testing and help account for systemic biases in clinical trials. Policies are needed to ensure this technology is adopted responsibly, and to address ethical concerns around patient consent and donor anonymisation.

Keywords Miniaturised organs · organoids · clinical trials · drug development

Aim and Objectives

The aim of this article is to outline applications of testing drugs on miniaturised organs and to discuss the implications this technology has for policy. The benefits of this technology in drug development and clinical trials will be evaluated, followed by a discussion of related ethical concerns. Policy recommendations will then be made to address these concerns and promote a positive impact of this technology.

Scientific Background

Drug development is a lengthy and expensive process (Figure 1) [1, 2]. Candidate drugs are

discovered and developed, then undergo animal testing in pre-clinical trials to investigate safety and the effects of the drug on a living organism. If these results are promising, the safety and efficacy of the drug is tested with human subjects in clinical trials before regulatory approval.

Advances in chemistry and biology have improved the design and synthesis of medicines. However, testing the safety and efficacy of new drugs remains challenging. Testing drugs in animals has ethical considerations and it imprecisely models how the drug will affect humans [1, 2]. Additionally, drugs can have different efficacies and safety profiles in different people [3–11].

These issues may be addressed with the help of organoids and organs-on-chips, which are simplified, miniaturised humans organs (Figure 2) [12]. To grow organoids, adult human cells are reprogrammed into a stem cell, a type of progenitor cell that can develop into different cell types (Figure 2a). Stem cells are embedded in a gel where they divide and specialise into specific cell types, producing an organoid [13, 14]. Organs-on-chips are grown with a different approach. In the simplest form, a narrow tube containing a single cell type is used [15–17]. More complex systems can be fabricated with multiple types of cells separated by porous membranes (Figure 2b). Fluid can be pumped through the tubing for several purposes, such as mimicking blood flow.

One application of miniaturised organs is to test the safety and efficacy of drugs [15–20]. A limitation of animal models for drug testing is the difference between human and test animal biology, especially liver and kidney physiology [21–25]. Drugs are processed by the liver, producing by-products which are excreted by the kidneys into urine. Differences in human and test animal physiology mean that drugs may be processed and excreted differently [23–25]. For example, toxic by-products may be produced and accumulate in humans but not some animals [22–27].

As miniaturised organs are grown from human tissue, they can more closely mirror parts of human physiology than test animals [28–36]. Testing medicines on miniaturised organs could therefore provide safety and efficacy data that animal models cannot [28–32, 35–41]. However, animal models remain the only method to study drugs in living organisms with fully grown, interconnected organ systems before human trials. Both testing methods therefore have their advantages. Miniaturised organ testing could be used to screen drugs prior to animal testing and, as the technology advances, could further complement and replace aspects of animal testing [13–16, 19, 28, 35, 42]. The ideal outcome, which policy should support, is more efficient drug development that delivers safer and more effective drug candidates with reduced animal use.

Policy Implications

Policies and regulations that outline how testing drugs on miniaturised organs can be considered in the drug development process are required. Miniaturised organ testing may identify safety or efficacy concerns that would remain unidentified until animal or human trials [14–16, 42, 43]. This approach would address a demand for the reduction of animal testing by medical and regulatory agencies, including the European Medicines Agency (EMA) [29, 30, 44–48]. However, uncertainty regarding how these technologies will be considered by regulators is hampering the adoption of miniaturised organ testing. The EMA states: "... the uptake of these newer models [miniaturised organ testing] in marketing authorisation submissions has not been high ... One reason for hesitancy may be concerns ... that use of such New Approach Methodologies (NAMs) will not be acceptable to regulators and will thus stall approvals ... Encouragement of these techniques is therefore needed" [46].

In addition to this apparent lack of clear regulatory guidelines, the EMA suggests that a lack of knowledge of such models and high implementation costs also play a role. If regulators outline how they would consider miniaturised organ testing, this could improve the confidence of pharmaceutical companies in this technology, increasing uptake.

Miniaturised organ testing can also help account for biases in clinical trials, which generally overrepresent men of European descent [3, 5]. While recent trials exhibit an improved gender balance, many groups remain underrepresented. The safety and efficacy of medicines are therefore not

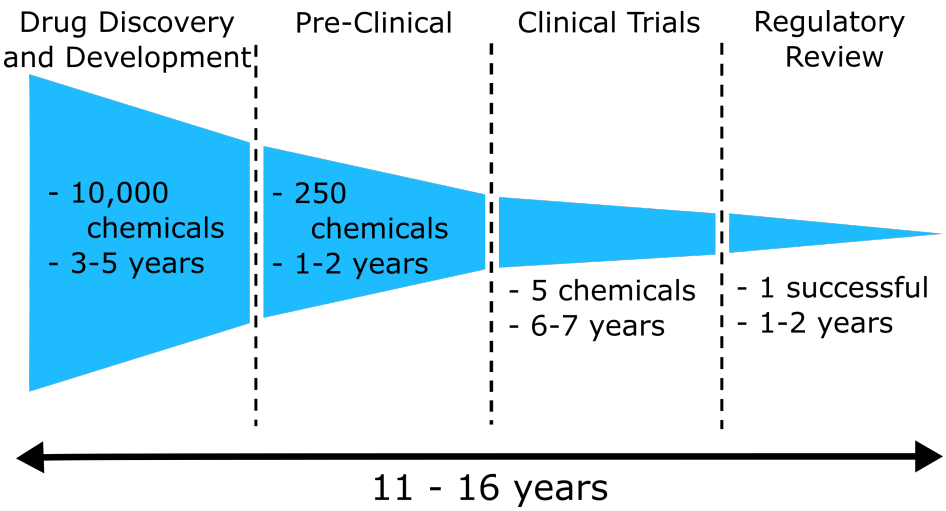

Figure 1: **Drug Discovery and Development Pipeline.** Overview of a traditional drug discovery and development pipeline with approximate values for the time taken and the number of chemicals at each stage. Figure adapted from Matthews et al. and Paul et al. [1, 2].

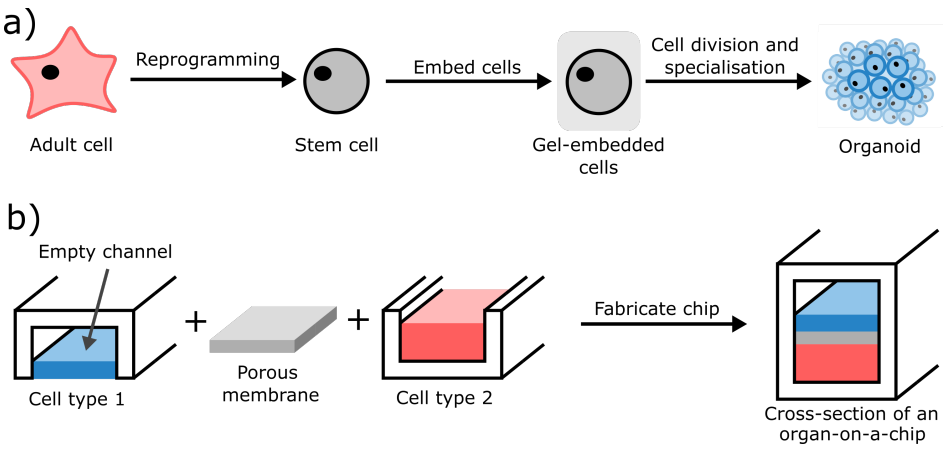

Figure 2: **The Construction of Organoids and Organ-on-Chips.** a) Organoids are grown by reprogramming an adult cell into a stem cell, which can specialise into different cell types under specific conditions. Stem cells are embedded into a gel that acts as a scaffold in which the stem cells divide, specialise, and grow into an organoid. b) An organ-on-a-chip containing two cell types. Two halves of a channel are prepared; one half containing a layer of one type of cell, and the other half containing another cell type. These halves are then connected with a porous membrane and the channel sealed. The resulting narrow tube has two cell types separated by a membrane, and an empty channel through which fluid can be passed.

assessed for all demographics equally. As a result, medical treatments may have different efficacies and safety profiles in women and ethnic minorities [3–11]. Using miniaturised organs derived from these underrepresented demographics could improve medical outcomes and help amend the existing biases in clinical trial populations. This approach is particularly relevant for completed clinical trials, whereas future clinical trials still require representative populations for the best medical outcomes.

Miniaturised organs also raise ethical challenges, particularly regarding the anonymisation of donations and the level of consent provided by donors [49–54]. Complete anonymisation of biological samples usually cannot be guaranteed, and re-identification may be preferred if research reveals health concerns the donor may face [49, 50, 54–57]. Donors should also explicitly consent to tissue collection and the specific uses of their tissue [51, 58]. Additionally, donors cannot give informed consent for all future uses of donated tissue when new applications are constantly discovered. An approach of ongoing consent may therefore be suitable where donors are contacted to consent for new uses of their tissues [49, 58, 59].

The European General Data Protection Regulation (GDPR) was updated in 2018 with implications for research involving stem cells, including miniaturised organ research [57]. However, biological samples face unique challenges such as the inability to definitively anonymise samples. Similar ethical and regulatory issues were faced by stem cell technology and many remain unresolved, despite regulations like the GDPR. Regulations which are specific for biological applications are therefore needed [57–62].

Policy Recommendations

The implementation of miniaturised organ technology faces several challenges as outlined above. Some brief recommendations for policy development in these areas are described:

Miniaturised Organ Testing in Drug Development

Regulators should outline what they consider to be important applications of miniaturised organ testing in drug development, and how these applications could be implemented alongside animal testing. For example, drug testing could be performed on liver organoids to identify toxic by-products prior to animal testing. Regulators should provide a roadmap detailing how miniaturised organ testing might be considered in the drug approval process as the technology develops.

Miniaturised Organ Testing for Historical Clinical Trials

Many previous clinical trial populations underrepresent women and ethnic minorities [3–11]. Pharmaceutical companies should be incentivised to test medicines on miniaturised organs derived from these underrepresented groups. One solution is to implement policies that extend patent protection of a therapeutic in exchange for performing this testing.

Consent and Anonymisation in Miniaturised Organs Technology

Policies addressing the ethical concerns arising from miniaturised organ technology should be developed. Anonymisation and consent are particularly important [49–51]. Donations should require informed consent and for the donor to be aware of what degree of anonymisation is possible [54]. The donor should also agree to conditions in which they will be re-identified or contacted if new uses of their donated tissue are desired, or research using their tissue suggests a particular health risk. In the latter case the decision to contact the donor should be rapid, aligned with the

donor's consent, and should involve the donor's primary healthcare provider if appropriate.

Conclusion

Miniaturised organ testing has the potential to make drug development more efficient and ethical, and to partially address historical biases in clinical trials. However, proactive policies and regulations are needed to promote the beneficial uptake of this technology and to limit ethical risks. Clear regulatory guidelines are required to give businesses confidence that miniaturised organ testing will be supported in drug development. Pharmaceutical companies should also be incentivised to perform miniaturised organ testing for drugs where clinical trials have been completed but involved unrepresentative populations. Yet, these benefits of using organoids are marred by ethical challenges. Proactively addressing these issues will best allow the benefits of this technology to be realised.

References

[1] H. Matthews, J. Hanison, and N. Nirmalan, ""Omics"-Informed Drug and Biomarker Discovery: Opportunities, Challenges and Future Perspectives," *Proteomes*, vol. 4, no. 3, p. 28, sep 2016. [Online]. Available: https://doi.org/10.3390/proteomes4030028

[2] S. M. Paul, D. S. Mytelka, C. T. Dunwiddie, C. C. Persinger, B. H. Munos, S. R. Lindborg, and A. L. Schacht, "How to improve RD productivity: The pharmaceutical industry's grand challenge," *Nat. Rev. Drug Discov.*, vol. 9, no. 3, pp. 203–214, mar 2010. [Online]. Available: https://doi.org/10.1038/nrd3078

[3] W. Batchelor, D. E. Kandzari, S. Davis, L. Tami, J. C. Wang, I. Othman, O. S. Gigliotti, A. Haghighat, S. Singh, M. Lopez, G. Giugliano, P. A. Horwitz, J. Chandrasekhar, P. Underwood, C. A. Thompson, and R. Mehran, "Outcomes in women and minorities compared with white men 1 year after everolimus-eluting stent implantation: Insights and results from the PLATINUM diversity and PROMUS element plus post-approval study pooled analysis," *JAMA Cardiol.*, vol. 2, no. 12, pp. 1303–1313, dec 2017. [Online]. Available: https://doi.org/10.1001/jamacardio.2017.3802

[4] S. E. Geller, A. R. Koch, P. Roesch, A. Filut, E. Hallgren, and M. Carnes, "The more things change, the more they stay the same: A study to evaluate compliance with inclusion and assessment of women and minorities in randomized controlled trials," *Acad. Med.*, vol. 93, no. 4, pp. 630–635, apr 2018. [Online]. Available: https://doi.org/10.1097/ACM.0000000000002027

[5] N. Eshera, H. Itana, L. Zhang, G. Soon, and E. O. Fadiran, "Demographics of clinical trials participants in pivotal clinical trials for new molecular entity drugs and biologics approved by FDA from 2010 to 2012," *Am. J. Ther.*, vol. 22, no. 6, pp. 435–455, nov/dec 2015. [Online]. Available: https://doi.org/10.1097/MJT.0000000000000177

[6] M. S. Khan, I. Shahid, T. J. Siddiqi, S. U. Khan, H. J. Warraich, S. J. Greene, J. Butler, and E. D. Michos, "Ten-Year Trends in Enrollment of Women and Minorities in Pivotal Trials Supporting Recent US Food and Drug Administration Approval of Novel Cardiometabolic Drugs," *J. Am. Heart Assoc.*, vol. 9, no. 11, p. e015594, jun 2020. [Online]. Available: https://doi.org/10.1161/JAHA.119.015594

[7] A. Chen, H. Wright, H. Itana, M. Elahi, A. Igun, G. Soon, A. R. Pariser, and E. O. Fadiran, "Representation of Women and Minorities in Clinical Trials for New Molecular Entities and Original Therapeutic Biologics Approved by FDA CDER from 2013 to 2015," *J. Women's Health*, vol. 27, no. 4, pp. 418–429, apr 2018. [Online]. Available: https://doi.org/10.1089/jwh.2016.6272

[8] O. P. Soldin and D. R. Mattison, "Sex differences in pharmacokinetics and pharmacodynamics," *Clinical Pharmacokinetics*,

vol. 48, no. 3, pp. 143–157, 2009. [Online]. Available: https://doi.org/10.2165/00003088-200948030-00001

[9] O. P. Soldin, S. H. Chung, and D. R. Mattison, "Sex differences in drug disposition," *Journal of Biomedicine and Biotechnology*, vol. 48, feb 2011. [Online]. Available: https://doi.org/10.1155/2011/187103

[10] A. J. Wood and H. H. Zhou, "Ethnic Differences in Drug Disposition and Responsiveness," *Clinical Pharmacokinetics*, vol. 20, no. 5, pp. 350–373, nov 1991. [Online]. Available: https://doi.org/10.2165/00003088-199120050-00002

[11] T. D. Bjornsson, J. A. Wagner, S. R. Donahue, D. Harper, A. Karim, M. S. Khouri, W. R. Murphy, K. Roman, D. Schneck, D. S. Sonnichsen, D. J. Stalker, S. D. Wise, S. Dombey, and C. Loew, "A Review and Assessment of Potential Sources of Ethnic Differences in Drug Responsiveness," *The Journal of Clinical Pharmacology*, vol. 43, no. 9, pp. 943–967, sep 2003. [Online]. Available: https://doi.org/10.1177/0091270003256065

[12] Z. Wang, X. He, H. Qiao, and P. Chen, "Global Trends of Organoid and Organ-On-a-Chip in the Past Decade: A Bibliometric and Comparative Study," *Tissue Eng. Part A*, vol. 26, no. 11-12, pp. 656–671, jun 2020. [Online]. Available: https://doi.org/10.1089/ten.tea.2019.0251

[13] H. C. Clevers, "Organoids: Avatars for Personalized Medicine," *Keio J. Med.*, vol. 68, no. 4, p. 95, 2019. [Online]. Available: https://doi.org/10.2302/kjm.68-006-ABST

[14] T. Takahashi, "Organoids for Drug Discovery and Personalized Medicine," *Annu. Rev. Pharmacol. Toxicol.*, vol. 59, pp. 447–462, 2019. [Online]. Available: https://doi.org/10.1146/annurev-pharmtox-010818-021108

[15] S. N. Bhatia and D. E. Ingber, "Microfluidic organs-on-chips," *Nat. Biotechnol.*, vol. 32, no. 8, pp. 760–772, aug 2014. [Online]. Available: https://doi.org/10.1038/nbt.2989

[16] E. W. Esch, A. Bahinski, and D. Huh, "Organs-on-chips at the frontiers of drug discovery," *Nat. Rev. Drug Discov.*, vol. 14, no. 4, pp. 248–260, apr 2015. [Online]. Available: https://doi.org/10.1038/nrd4539

[17] D. Huh, H. J. Kim, J. P. Fraser, D. E. Shea, M. Khan, A. Bahinski, G. A. Hamilton, and D. E. Ingber, "Microfabrication of human organs-on-chips," *Nat. Protoc.*, vol. 8, no. 11, pp. 2135–2157, oct 2013. [Online]. Available: https://doi.org/10.1038/nprot.2013.137

[18] J. Kondo and M. Inoue, "Application of Cancer Organoid Model for Drug Screening and Personalized Therapy," *Cells*, vol. 8, no. 5, p. 470, may 2019. [Online]. Available: https://doi.org/10.3390/cells8050470

[19] C. Liu, T. Qin, Y. Huang, Y. Li, G. Chen, and C. Sun, "Drug screening model meets cancer organoid technology," *Transl. Oncol.*, vol. 13, no. 11, p. 100840, nov 2020. [Online]. Available: https://doi.org/10.1016/j.tranon.2020.100840

[20] E. Driehuis, K. Kretzschmar, and H. Clevers, "Establishment of patient-derived cancer organoids for drug-screening applications," *Nat. Protoc.*, vol. 15, no. 10, pp. 3380–3409, oct 2020. [Online]. Available: https://doi.org/10.1038/s41596-020-0379-4

[21] G. A. Truskey, "Human Microphysiological Systems and Organoids as in Vitro Models for Toxicological Studies," *Front. Public Health*, vol. 6, p. 185, jul 2018. [Online]. Available: https://doi.org/10.3389/fpubh.2018.00185

[22] J. Kim, B. K. Koo, and J. A. Knoblich, "Human organoids: model systems for human biology and medicine," *Nat. Rev. Mol. Cell Biol.*, vol. 21, no. 10, pp. 571–584, oct 2020. [Online]. Available: https://doi.org/10.1038/s41580-020-0259-3

[23] J. T. Atkins, G. C. George, K. Hess, K. L. Marcelo-Lewis, Y. Yuan, G. Borthakur, S. Khozin, P. LoRusso, and D. S. Hong, "Pre-clinical animal models are poor predictors of human toxicities in phase 1 oncology clinical trials," *Br. J. Cancer*, vol. 123, no. 10, pp. 1496–1501, nov 2020. [Online]. Available: https://doi.org/10.1038/s41416-020-01033-x

[24] M. Martignoni, G. M. M. Groothuis, and R. de Kanter, "Species differences between mouse, rat, dog, monkey and

human CYP-mediated drug metabolism, inhibition and induction," *Expert Opin. Drug Metab. Toxicol.*, vol. 2, no. 6, pp. 875–894, dec 2006. [Online]. Available: https://doi.org/10.1517/17425255.2.6.875

[25] K. Susztak, M. Bitzer, T. W. Meyer, and T. H. Hostetter, "Animal models of renal disease," *Kidney Int.*, vol. 73, no. 5, pp. 526–528, mar 2008. [Online]. Available: https://doi.org/10.1038/sj.ki.5002724

[26] D. A. Smith and R. S. Obach, "Metabolites and Safety: What Are the Concerns, and How Should We Address Them?" *Chem. Res. Toxicol.*, vol. 19, pp. 1570–1579, oct 2006. [Online]. Available: https://doi.org/10.1021/tx0602012

[27] J. E. May, J. Xu, H. R. Morse, N. D. Avent, and C. Donaldson, "Toxicity testing: The search for an in vitro alternative to animal testing," *Br. J. Biomed. Sci.*, vol. 66, no. 3, pp. 160–165, may 2009. [Online]. Available: https://doi.org/10.1080/09674845.2009.11730265

[28] M. Huch, J. A. Knoblich, M. P. Lutolf, and A. Martinez-Arias, "The hope and the hype of organoid research," *Development*, vol. 144, no. 6, pp. 938–941, mar 2017. [Online]. Available: https://doi.org/10.1242/dev.150201

[29] R. Ltd., "Roche - replacing animal testing," https://www.roche.com/research_and_development/who_we_are_how_we_work/ethics_in_rd/animal_research/developing-alternatives-to-animal-testing.htm, 2020, accessed: 18.11.2020.

[30] R. C. Dutta and A. K. Dutta, "Human-Organoid Models: Accomplishments to Salvage Test-Animals," *J. Biomed. Eng. Med. Devic.*, vol. 1, no. 2, p. 1000110, may 2016. [Online]. Available: https://doi.org/10.4172/2475-7586.1000110

[31] J. Theobald, A. Ghanem, P. Wallisch, A. A. Banaeiyan, M. A. Andrade-Navarro, K. Taškova, M. Haltmeier, A. Kurtz, H. Becker, S. Reuter, R. Mrowka, X. Cheng, and S. Wölfl, "Liver-Kidney-on-Chip to Study Toxicity of Drug Metabolites," *ACS Biomater. Sci. Eng.*, vol. 4, no. 1, pp. 78–89, jan 2018. [Online]. Available: https://doi.org/10.1021/acsbiomaterials.7b00417

[32] D. Vyas, P. M. Baptista, M. Brovold, E. Moran, B. Gaston, C. Booth, M. Samuel, A. Atala, and S. Soker, "Self-assembled liver organoids recapitulate hepatobiliary organogenesis in vitro," *Hepatology*, vol. 67, no. 2, pp. 750–761, feb 2018. [Online]. Available: https://doi.org/10.1002/hep.29483

[33] L. Sun and L. Hui, "Progress in human liver organoids," *J. Mol. Cell Biol.*, vol. 12, no. 8, pp. 607–617, aug 2020. [Online]. Available: https://doi.org/10.1093/jmcb/mjaa013

[34] M. Takasato, P. X. Er, H. S. Chiu, B. Maier, G. J. Baillie, C. Ferguson, R. G. Parton, E. J. Wolvetang, M. S. Roost, S. M. De Sousa Lopes, and M. H. Little, "Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis," *Nature*, vol. 526, no. 7574, pp. 564–568, oct 2015. [Online]. Available: https://doi.org/10.1038/nature15695

[35] R. Nishinakamura, "Human kidney organoids: progress and remaining challenges," *Nat. Rev. Nephrol.*, vol. 15, no. 10, pp. 613–624, oct 2019. [Online]. Available: https://doi.org/10.1038/s41581-019-0176-x

[36] B. Ding, G. Sun, S. Liu, E. Peng, M. Wan, L. Chen, J. Jackson, and A. Atala, "Three-dimensional renal organoids from whole kidney cells: Generation, optimization, and potential application in nephrotoxicology in vitro," *Cell Transplant.*, vol. 29, pp. 1–10, mar 2020. [Online]. Available: https://doi.org/10.1177/0963689719897066

[37] T. Shinozawa, M. Kimura, Y. Cai, N. Saiki, Y. Yoneyama, R. Ouchi, H. Koike, M. Maezawa, R.-R. Zhang, A. Dunn, A. Ferguson, S. Togo, K. Lewis, W. L. Thompson, A. Asai, and T. Takebe, "High-Fidelity Drug-Induced Liver Injury Screen Using Human Pluripotent Stem Cell–Derived Organoids," *Gastroenterology*, vol. 160, no. 3, pp. 831–846.e10, feb 2021. [Online]. Available: https://doi.org/10.1053/j.gastro.2020.10.002

[38] J. F. Dekkers, G. Berkers, E. Kruisselbrink, A. Vonk, H. R. De Jonge, H. M. Janssens, I. Bronsveld, E. A. Van De Graaf, E. E. Nieuwenhuis, R. H. Houwen, F. P. Vleggaar, J. C. Escher, Y. B. De Rijke, C. J. Majoor, H. G. Heijerman, K. M. De Winter-De Groot, H. Clevers, C. K.

Van Der Ent, and J. M. Beekman, "Characterizing responses to CFTR-modulating drugs using rectal organoids derived from subjects with cystic fibrosis," *Sci. Transl. Med.*, vol. 8, no. 344, pp. 344ra84–344ra84, jun 2016. [Online]. Available: https://doi.org/10.1126/scitranslmed.aad8278

[39] N. Prior, P. Inacio, and M. Huch, "Liver organoids: From basic research to therapeutic applications," *Gut*, vol. 68, no. 12, pp. 2228–2237, dec 2019. [Online]. Available: https://doi.org/10.1136/gutjnl-2019-319256

[40] R. Morizane and J. V. Bonventre, "Kidney Organoids: A Translational Journey," *Trends Mol. Med.*, vol. 23, no. 3, pp. 246–263, mar 2017. [Online]. Available: https://doi.org/10.1016/j.molmed.2017.01.001

[41] J. Y. Lee, H. J. Han, S. J. Lee, E. H. Cho, H. B. Lee, J. H. Seok, H. S. Lim, and W. C. Son, "Use of 3D human liver organoids to predict drug-induced phospholipidosis," *Int. J. Mol. Sci.*, vol. 21, no. 8, apr 2020. [Online]. Available: https://doi.org/10.3390/ijms21082982

[42] D. Tuveson and H. Clevers, "Cancer modeling meets human organoid technology," *Science*, vol. 364, no. 6444, pp. 952–955, jun 2019. [Online]. Available: https://doi.org/10.1126/science.aaw6985

[43] T. Grabinger, L. Luks, F. Kostadinova, C. Zimberlin, J. P. Medema, M. Leist, and T. Brunner, "Ex vivo culture of intestinal crypt organoids as a model system for assessing cell death induction in intestinal epithelial cells and enteropathy," *Cell Death Dis.*, vol. 5, no. 5, pp. e1228–e1228, may 2014. [Online]. Available: https://doi.org/10.1038/cddis.2014.183

[44] EMA, "Ethical use of animals in medicine testing," https://www.ema.europa.eu/en/human-regulatory/research-development/ethical-use-animals-medicine-testing, accessed: 18 November 2020.

[45] FDA, "Food and drug administration's predictive toxicology roadmap 2018 annual report," https://www.fda.gov/science-research/about-science-research-fda/fdas-predictive-toxicology-roadmap, accessed: 2020-11-17.

[46] "EMA Regulatory Science to 2025 Strategic reflection," European Medicines Agency, Tech. Rep., 2020. [Online]. Available: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

[47] K.Morris, "Emulate signs collaborative agreement with the fda to apply lung-chip to evaluate safety of covid-19 vaccines and protective immunity against sars-cov-2," https://www.biospace.com/article/releases/emulate-signs-collaborative-agreement-with-the-fda-to-apply-lung-chip-to-evaluate-safety-of-covid-19-vaccines-and-protective-immunity-against-sars-cov-2/, 2020, accessed: 17 Nov 2020.

[48] "Working to reduce the use of animals in scientific research 2 Delivering our Commitment to Replace, Reduce and Refine the Use of Animals in Research," Home Office Animals in Science Regulation Unit; Department for Business, Innovation and Skills; Government Office for Science, London, Tech. Rep., 2014. [Online]. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/277942/bis-14-589-working-to-reduce-the-use-of_animals-in-research.pdf

[49] S. N. Boers, J. J. Delden, H. Clevers, and A. L. Bredenoord, "Organoid biobanking: identifying the ethics," *EMBO rep.*, vol. 17, no. 7, pp. 938–941, jul 2016. [Online]. Available: https://doi.org/10.15252/embr.201642613

[50] S. N. Boers and A. L. Bredenoord, "Consent for governance in the ethical use of organoids comment," *Nat. Cell Biol.*, vol. 20, no. 6, pp. 642–645, jun 2018. [Online]. Available: https://doi.org/10.1038/s41556-018-0112-5

[51] M. Munsie, I. Hyun, and J. Sugarman, "Ethical issues in human organoid and gastruloid research," *Development*, vol. 144, no. 6, pp. 942–945, mar 2017. [Online]. Available: https://doi.org/10.1242/dev.140111

[52] A. Lavazza and M. Massimini, "Cerebral organoids: Ethical issues and consciousness assessment," *J. Med. Ethics*, vol. 44, no. 9, pp. 606–610, sep 2018. [Online]. Available: https://doi.org/10.1136/medethics-2017-104555

[53] A. L. Bredenoord, H. Clevers, and J. A. Knoblich, "Human tissues in a dish: The research and ethical implications of organoid technology," *Science*, vol. 355, no. 6322, p. eaaf9414, jan 2017. [Online]. Available: https://doi.org/10.1126/science.aaf9414

[54] U. Ogbogu, S. Burningham, A. Ollenberger, K. Calder, L. Du, K. El Emam, R. Hyde-Lay, R. Isasi, Y. Joly, I. Kerr, B. Malin, M. McDonald, S. Penney, G. Piat, D. C. Roy, J. Sugarman, S. Vercauteren, G. Verhenneman, L. West, and T. Caulfield, "Policy recommendations for addressing privacy challenges associated with cell-based research and interventions," *BMC Med. Ethics*, vol. 15, no. 1, p. 7, feb 2014. [Online]. Available: https://doi.org/10.1186/1472-6939-15-7

[55] B. M. Knoppers and R. Isasi, "Stem cell banking: Between traceability and identifiability," *Genome Med.*, vol. 2, no. 10, p. 73, oct 2010. [Online]. Available: https://doi.org/10.1186/gm194

[56] R. Isasi, P. W. Andrews, J. M. Baltz, A. L. Bredenoord, P. Burton, I. M. Chiu, S. C. Hull, J. W. Jung, A. Kurtz, G. Lomax, T. Ludwig, M. McDonald, C. Morris, H. H. Ng, H. Rooke, A. Sharma, G. N. Stacey, C. Williams, F. Zeng, and B. M. Knoppers, "Identifiability and privacy in pluripotent stem cell research," *Cell Stem Cell*, vol. 14, no. 4, pp. 427–430, apr 2014. [Online]. Available: https://doi.org/10.1016/j.stem.2014.03.014

[57] M. Morrison, J. Bell, C. George, S. Harmon, M. Munsie, and J. Kaye, "The European General Data Protection Regulation: Challenges and considerations for iPSC researchers and biobanks," *Regen. Med.*, vol. 12, no. 6, pp. 693–703, sep 2017. [Online]. Available: https://doi.org/10.2217/rme-2017-0068

[58] K. Aalto-Setälä, B. R. Conklin, and B. Lo, "Obtaining Consent for Future Research with Induced Pluripotent Cells: Opportunities and Challenges," *PLoS Biol.*, vol. 7, no. 2, p. e1000042, feb 2009. [Online]. Available: https://dx.plos.org/10.1371/journal.pbio.1000042

[59] A. Cambon-Thomsen, E. Rial-Sebbag, and B. M. Knoppers, "Trends in ethical and legal frameworks for the use of human biobanks," *Eur. Respir. J.*, vol. 30, no. 2, pp. 373–382, aug 2007. [Online]. Available: https://doi.org/10.1183/09031936.00165006

[60] J. Kimmelman, I. Hyun, N. Benvenisty, T. Caulfield, H. E. Heslop, C. E. Murry, D. Sipp, L. Studer, J. Sugarman, and G. Q. Daley, "Policy: Global standards for stem-cell research," *Nature*, vol. 533, no. 7603, pp. 311–313, may 2016. [Online]. Available: https://doi.org/10.1038/533311a

[61] B. George, "Regulations and guidelines governing stem cell based products: Clinical considerations," *Perspect. Clin. Res.*, vol. 2, no. 3, p. 94, jul 2011. [Online]. Available: https://doi.org/10.4103/2229-3485.83228

[62] M. Reisman and K. T. Adams, "Stem cell therapy: A look at current research, regulations, and remaining hurdles," *P and T*, vol. 39, no. 12, pp. 846–857, dec 2014. [Online]. Available: https://www-ncbi-nlm-nih-gov.ezp.lib.cam.ac.uk/pmc/articles/PMC4264671/

About the Author

Tim Chisholm is a 3rd year PhD student in the Department of Chemistry at the University of Cambridge, researching new amyloid-binding ligands for studying dementia. A key focus of his research is to work towards developing accurate and accessible tools for diagnosing dementia. Previously he received an undergraduate and master's degree from the University of Sydney where he worked on improving chemical peptide synthesis using photochemistry and flow chemistry. He can be contacted at `tsc42@cam.ac.uk`.

Conflict of interest The Author declares no conflict of interest.